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Copper and triphenylphosphine-promoted sulfenylation of quinones with arylsulfonyl chlorides

*Xiaoli Yu, Qiujin Wu, Huida Wan, Zhaojun Xu, Xingle Xu and Dawei Wang**

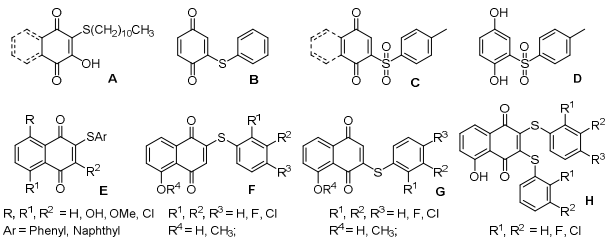
The Key Laboratory of Food Colloids and Biotechnology, Ministry of Education, School of Chemical and Material Engineering, Jiangnan University, Wuxi 214122, Jiangsu Province, China.

wangdw@jiangnan.edu.cn

Abstract: The efficient copper and triphenylphosphine-promoted sulfenylation of quinones with arylsulfonyl chlorides has been developed under mild conditions with moderate to good yields. Significantly, this provides an alternative method to synthesis of arylthioquinone derivatives. There is the first time to prepare arylthioquinones with arylsulfonyl chlorides as starting material, which avoids the use of awful smell of thioalcohols and thiophenols.

Quinone is a common and unique medical intermediate and building blocks for the biologically natural products, such as antibiotic, pharmaceuticals, dyestuff, anticancer, pesticides and pigments for their special properties.[1] Among this, arylthioquinone is a typical example,[2] Tandon and coworkers reported that 2-methylsulfanyl-[1,4]naphtha quinone showed excellent fungistatic activity, which results in a marked increase in its activity profile.[3a] While the compounds **E** were found as antifungal agents as they possess in vitro activity against several fungal cultures capable of causing disease in vertibrates (Scheme 1).[3b] Ryu *et al* reported that 2/3-arylthio- and 2,3-bis(arylthio)-5-hydroxy-/5-methoxy-1,4-naphthoquin-ones were tested for in vitro antifungal activity against *Candida albicans*, *C. tropicalis*. and *Aspergillus niger*.[4]

Scheme 1. Several biological arylthioquinones.



Arylthioquinone derivatives were usually prepared from the quinones and thiophenols.[5] Recently, we developed copper-catalyzed cascade reaction of thiophenol hydroxylation and S-arylation to prepare arylthioquinones derivatives through disulfide-directed C-H activation in two steps method.[6d] However, the awful smell of thioalcohols and thiophenols is unsufferable and sometimes limits their applications. Therefore, searching for alternative reagents for thioalcohols and thiophenols is still an interesting and scientific issue. Chemists have paid great efforts to this area. Several kinds of alternative reagents are proved to be effective to sulfenylation transformations. Sulfonyl hydrazides,[7] N-(thiophenyl) succinimide,[8] sodium sulfinates,[9] sulfinic acids[10] and arylsulfonyl chlorides are good choice to avoid the upper shortcomings for the cheap or no bad smell nature.[11] In 2011, You and co-workers reported an organomediated-sulfenylation of (hetero)arenes to synthesize di(hetero)arylthioethers by directly using inexpensive and easily available arylsulfonyl chlorides as an alternative sulfur source (Scheme 2).[12] Later, Zheng *et al* described a method to parpare 1-methyl-3-(arylthio)-1H-indoles by the photoredox reactions of N-methylindoles with readily available arylsulfonyl chlorides in moderate yields.[13] Adimurthy *et al* developed copper-catalyzed regioselective C-3 sulfenylation of imidazo[1,2-a]pyridines using *p*-tosylchloride as a benign source of sulfenylating agents.[14] Wu and Zou reported a copper-catalyzed regioselective sulfenylation of indoles with arylsulfonyl chlorides, which provides a good method to a series of structurally diverse indole thioethers with high regioselectivity.[15] Recently, Deng and co-workers developed an iodine-promoted method for the synthesis of 2-arylsulfanylphenols using cyclohexanones as a reliable phenol source with various sulfonyl chlorides and sodium sulfinates as the sulfur source.[16] Zhou *et al*

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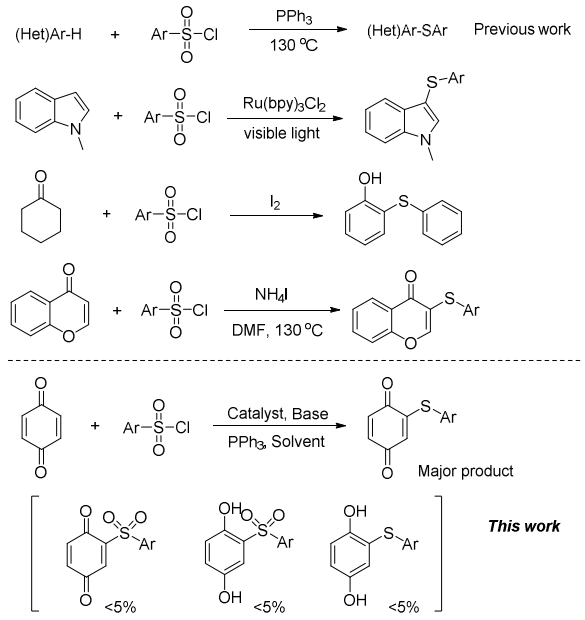
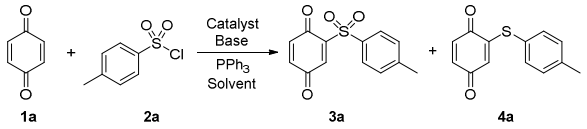
reported a regioselective and novel ammonium iodide mediated C-S bond formation protocol involving flavones and sulfonyl chlorides.[17] From all the aforementioned excellent examples, we found that the commercially available arylsulfonyl chlorides were proved to be promising sulfenylation reagents with the accessibility, substrate compatibility and stability. Therefore, more transformations are needed to explore with arylsulfonyl chlorides as sulfenylation reagents. Based on our previous research on quinone derivatives synthesis,[6] herein, we reported the sulfenylation of quinones with arylsulfonyl chlorides under copper and triphenylphosphine conditions in moderate to good yields. Significantly, this provides an alternative method to synthesis of arylthioquinone derivatives. To the best of our knowledge, there is the first time to prepare arylthioquinones with arylsulfonyl chlorides as starting material, which avoids the use of awful smell of thioalcohols and thiophenols.

Scheme 2. Sulfenylation reactions with arylsulfonyl chlorides as sulfur source.



To start the research, benzoquinone and 4-methylbenzenesulfonyl chloride were selected as model substrates to attempt the reaction with palladium as a catalyst and triphenylphosphine as a reducing agent. However, it was found that only a reaction mixture was achieved (Table 1, entry 3). To our pleased, moderate yield of sulfenylation product was achieved when CuI was added to the reaction mixture instead of palladium catalyst (Table 1, entry 6). For a higher yield, a series of screening reaction conditions were carried on. Firstly, toluene was screened to be more profitable in this reaction than 1,2-dichroethane. Then several other copper catalysts were explored for their influence on the reaction behavior. However, there were no better catalysts than CuI. Others conditions, like base, were also screened (Table 1, entries 13-16). Several other reductants were tested for this transformation (Table 1, entries 15, 19-21). It was found that $P(OMe)_3$ and Et_3SiH could not promote this reaction, while $P(nBu)_3$ produce a slightly lower yield (72%) than PPh_3. The best reaction conditions were obtained as follows: CuI as the catalyst, K_3PO_4 as the base, PPh_3 as the reducing agent and toluene as the solvent. It should be noted that the reaction could not happen without phosphorus reagent (Table 1, entry 17). Only low yield was achieved without of copper as a catalyst under triphenylphosphine condition (Table 1, entry 18).

Table 1. Screening of optimized reaction conditions [a]



Entry	Catalyst	Base	Solvent	**3a**[%][b,c]	**4a**[%][b,c]
1	$Pd(OAc)_2$	K_2CO_3	DCE	89	<5[d]
2	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	K_2CO_3	DCE	85	<5[d]
3	$Pd(OAc)_2$	K_2CO_3	DCE	26	37
4	$[Cp^*RhCl_2]_2$	K_2CO_3	DCE	33	18
5	$Pd(OAc)_2$/CuI	K_2CO_3	DCE	12	43
6	CuI	K_2CO_3	DCE	<5	61
7	CuI	K_2CO_3	DCM	<5	<5
8	CuI	K_2CO_3	DCE	<5	<5[e]
9	CuI	K_2CO_3	Toluene	<5	65
10	CuI	Cs_2CO_3	Toluene	<5	73
11	CuCl	Cs_2CO_3	Toluene	<5	59
12	$Cu(OAc)_2$	Cs_2CO_3	Toluene	<5	47
13	$CuSO_4$	Cs_2CO_3	Toluene	<5	62
14	CuI	*t*BuOK	Toluene	<5	11
15	CuI	K_3PO_4	Toluene	<5	78
16	CuI	KOH	Toluene	<5	<5
17	CuI	K_3PO_4	Toluene	<5	-[d]
18	-	K_3PO_4	Toluene	<5	47
19	CuI	K_3PO_4	Toluene	<5	<5[f]

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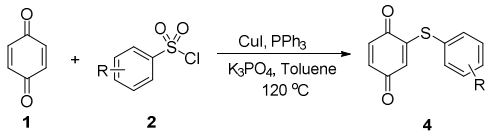
20	CuI	K_3PO_4	Toluene	<5	72[g]
21	CuI	K_3PO_4	Toluene	<5	<5[h]
22	CuI	K_3PO_4	MeCN	<5	74
23	CuI	K_3PO_4	Dioxane	<5	39
24	CuI	K_3PO_4	THF	<5	37
25	CuI	K_3PO_4	DMF	<5	<5
26	-	K_3PO_4	Toluene	12	19
27	CuI	-	Toluene	17	26
28	-	-	Toluene	<5	<5

[a] Reagents and conditions: **1a** (1.0 mmol), **2a** (2.5 mmol), catalyst (10 mol%), base (1.5 mmol), PPh_3 (2.5 mmol), solvent (5 mL), reflux, 10-24 h. [b] Yields of isolated product. [c] **5a** and **6a** were not checked". [d] Without PPh_3. [e] 40 °C. [f] $P(OMe)_3$. [g] $P(nBu)_3$. [h] Et_3SiH.

Subsequently, under the optimal conditions, we explored the scope of arylthioquinones synthesis from quinones with arylsulfonyl chlorides and the results are summarized in Table 2. The reactions were carried out at reflux temperature over a period of 10 hours each, with exposure to the air. Generally, nearly all the starting materials were converted to the arylthioquinones with moderate to good yields. As shown in Table 2, methyl-, chloro- and fluoro-substituted arylthioquinones were obtained in 46%-83% yields. The substrate with electron-withdrawing substituents gave desired products at almost similar yields relative to that obtained from substrates with electron-donating substituents. The best yield was obtained when the substrate with *t*Bu group in the substrate (Table 2, entry 12). Interestingly, the system could tolerate the methoxy, nitro, trifluoromethyl groups and all these substrates were transformed to the corresponding arylthioquinone derivatives with moderate to good yields (Table 2, entries13-18).

Table 2. Substrate expansion experiments [a]



Entry	R	Yield [%] [b]
1	4-Me	78 (**4a**)
2	4-H	74 (**4b**)
3	4-Et	71 (**4c**)
4	3-Me	68 (**4d**)
5	4-F	79 (**4e**)
6	4-Cl	81 (**4f**)
7	4-Br	77 (**4g**)
8	2-Br	76 (**4h**)
9	3-Cl	63 (**4i**)
10	2,6-Cl	52 (**4j**)
11	2-F	71 (**4k**)
12	4-*t*Bu	83 (**4l**)
13	4-OMe	79 (**4m**)
14	3-OMe	82 (**4n**)
15	2-OMe	74 (**4o**)
16	3,4-OMe	83 (**4p**)
17	4-NO_2	64 (**4q**)
18	4-CF_3	72 (**4r**)

[a] Reagents and conditions: **1** (1.0 mmol), **2** (2.5 mmol), CuI (10 mol%), K_3PO_4 (1.5 mmol), PPh_3 (2.5 mmol), toluene (5 mL), 10 h, 120 °C. [b] Yields of isolated product.

Recently, Deng and co-workers reported the iodine-promoted method for the synthesis of 2-arylsulfanylphenols,[16a] while only arylthioquinone derivatives were separated with this methodology here after screening of reaction conditions, which maybe attribute to the suitable stability of quinones.

Finally, a possible reaction pathway for this reaction was proposed (Scheme 3). It was reported to produce sulfonyl-quinones under palladium conditions,[6a] while arylsulfenyl chloride (PhSCl) was formed, when sulfonyl chlorides were dealt with triphenylphosphine as reductive reagents.[12] Next, the intermediate B, which might be formed with the help of base through Baylis-Hillman process, reacted with arylsulfenyl chloride to produce arylthioquinone derivatives.

Scheme 3. The proposed possible reaction passway.

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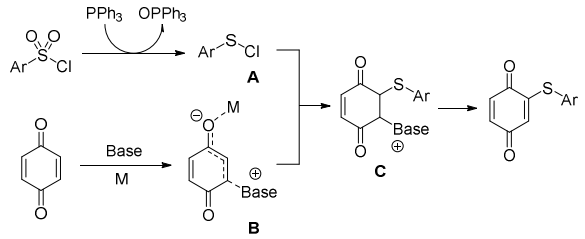

Conclusions

In conclusion, the efficient sulfenylation reaction of quinones with arylsulfonyl chlorides has been developed under copper and triphenylphosphine conditions with moderate to good yields. Significantly, this provides an alternative method to synthesis of arylthioquinone derivatives.

Supporting Information

Detailed experimental procedures, ^{1}H NMR, ^{13}C NMR data for **4a-4r**. This material is available free of charge via the Internet.

Acknowledgements

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References

1. (a) J. T. Tsay, W. Oh, T. J. Larson, S. Jackowski and C. O. Rock, *J. Biol. Chem*. 1992, **267**, 6807. (b) X. Qiu, C. A. Janson, A. K. Konstantinidis, S. Nwagwu, C. Silverman, W. W. Smith, S. Khandekar, J. Lonsdale and S. S. Abdel-Meguid, *J. Biol. Chem.* 1999, **274**, 36465. (c) W. P. Revill, M. J. Bibb, A. K. Scheu, H. J. Kieser and D. A. Hopwood, *J. Bacteriol.* 2001, **183**, 3526. (d) M. Alhamadsheh, N. Waters, S. Sachdeva, P. Lee and K. Reynolds, *Bioorg. Med. Chem. Lett.* 2008, **18**, 6402.
2. (a) G. A. Kraus and I. Kim, *J. Org. Chem*. 2003, **68**, 4517. (b) C.-K. Ryu, J.-Y. Shim, M. J. Chae, I. H. Choi, J.-Y. Han, O.-J. Jung, J. Y. Lee and S. H. Jeong, *Eur. J. Med. Chem.* 2005, **40**, 438. (c) B. J. Mulchin, C. G. Newton, J. W. Baty, C. H. Grasso, W. J. Martin, M. C. Walton, E. M. Dangerfield, C. H. Plunkett, M. V. Berridge, J. L. Harper, M. S. M. Timmer and B. L. Stocker, *Bioorg. Med. Chem.* 2010, **18**, 3238.
3. (a) V. K. Tandon, R. B. Chhor, R. V. Singh, S. Rai and D. B. Yadav, *Bioorg. Med. Chem. Lett.* 2004, **14**, 1079. (b) V. K. Tandon, R. V.Singh and D. B. Adav, *Bioorg. Med. Chem. Lett.* 2004, **14**, 2091. (c) V. K. Tandon and H. K. Maurya, *Tetrahedron Lett*. 2009, **50**, 5896.
4. C.-K. Ryu, J.-Y. Shim, M. J. Chae, I. H. Choi, J.-Y. Han, O.-J. Jung, J. Y. Lee and S. H. Jeong, *Eur. J. Med. Chem.* 2005, **40**, 438.
5. (a) M. C. Carreno, G. Ruano, A. Urbano, C. Z. Remor and Y. Arroyo, *J. Org. Chem*. 2000, **65**, 453. (b) C.-K. Ryu, I. H. Choi and R. E. Park, *Syn. Common.* 2006, **36**, 3319.
6. For selected quinone transformations in our group, see: (a) B. Ge, D. Wang, W. Dong, P. Ma, Y. Li and Y. Ding, *Tetrahedron Lett*. 2014, **55**, 5443. (b) D. Wang, B. Ge, L. Du, H. Miao and Y. Ding, *Synlett*, 2014, **25**, 2895. (c) D. Wang, B. Ge, L. Li, J. Shan and Y. Ding, *J. Org. Chem.* 2014, **79**, 8607. (d) D. Wang, X. Yu, W. Yao, W. Hu, C. Ge and X. Shi, *Chem. Eur. J.* 2016, **22**, 5543.
7. (a) F.-L. Yang and S.-K. Tian, *Angew. Chem. Int. Ed.* 2013, **52**, 4929. (b) A. K. Bagdi, S. Mitra, M. Ghosh and A. Hajra, *Org. Biomol. Chem.*, 2015, **13**, 3314. (c) R. Rahaman, N. Devi, K. Sarma and P. Barman, *RSC Adv.*, 2016, **6**, 10873.
8. (a) M. Tudge, M. Tamiya, C. Savarin and G. R. Humphrey, *Org. Lett*. 2006, **8**, 565. (b) C. C. Silveira, S. R. Mendes, L. Wolf and G. M. Martins, *Tetrahedron Lett*. 2010, **51**, 2014. (c) T. Hostier, V. Ferey, G. Ricci, D. G. Pardoa and J. Cossy, *Chem. Commun.,* 2015, **51**, 13898.
9. (a) Y.-M. Lin, G.-P. Lu, C. Cai and W.-B. Yi, *Org. Lett.* 2015, **17**, 3310. (b) D. Wang, R. Zhang, S. Lin, Zh. Yan and S. Guo, *RSC Adv.*, 2015, **5**, 108030. (c) F. Xiao, S. Chen, J. Tian, H. Huang, Y. Liu and G.-J. Deng, *Green Chem.*, 2016, **18**, 1538. (d) Y. Gao, Y. Gao, X. Tang, J. Peng, M. Hu, W. Wu and H. Jiang, *Org. Lett.* 2016, **18**, 1158. (e) C. Wang, H. Jia, Z. Li, H. Zhang and B. Zhao, *RSC Adv.*, 2016, **6**, 21814.
10. (a) C.-R. Liu and L.-H. Ding, *Org. Biomol. Chem.*, 2015, **13**, 2251. (b) R. Rahaman, N. Devi, J. R. Bhagawati and P. Barman, *RSC Adv.*, 2016, **6**, 18929.
11. (a) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. A. Hor and X. Liu, *Chem. Soc. Rev.,* 2015, **44**, 291. (b) G. Kumaraswamy, R. Rajua and V. Narayanaraoa, *RSC Adv.*, 2015, **5**, 22718.
12. (a) Q. Wu, D. Zhao, X. Qin, J. Lan and J. You, *Chem. Commun.* 2011, **47**, 9188. (b) D. Wan, Y. Yang, X. Liu, M. Li, S. Zhao and J. You, *Eur. J. Org. Chem.* 2016, 55.
13. M. Chen, Z.-T. Huang and Q.-Y. Zheng, *Chem. Commun.* 2012, **48**, 11686.
14. C. Ravi, D. C. Mohan and S. Adimurthy, *Org. Biomol. Chem.*, 2016, **14**, 2282.
15. Z. Wu, Y.-C. Li, W.-Z. Ding, T. Zhu, S.-Z. Liu and L.-H. Zou, *Asian J. Org. Chem.* 2016, **5**, 625.
16. (a) Y. Chen, F. Xiao, H. Chen, S. Liu and G.-J. Deng, *RSC Adv.*, 2014, **4**, 44621. (b) F.-H. Xiao, H. Xie, S.-W. Liu and G.-J. Deng, *Adv. Synth. Catal.*, 2014, ***356***, 364.
17. W. Zhao and A. Zhou, *ChemCatChem* 2015, **7**, 3464.

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Graphical Abstract

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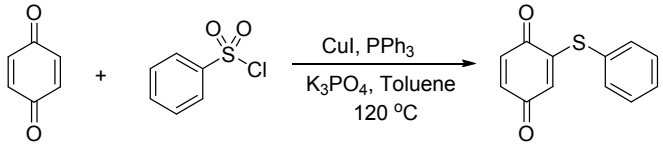
Xiaoli Yu, Qiujin Wu, Huida Wan, Zhaojun Xu, Xingle Xu and Dawei Wang*

The Key Laboratory of Food Colloids and Biotechnology, Ministry of Education, School of Chemical and Material Engineering, Jiangnan University, Wuxi 214122, Jiangsu Province, China.



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